Report of the ICCR Joint Ad Hoc Working Group on Nanotechnology in Cosmetic Products:

Criteria and Methods of Detection

ICCR-4

Toronto, Canada
July 14, 2010

Guidance document created by the ICCR initiative intended to help determine if a specific material used in cosmetics is considered a "nanomaterial" for regulatory purposes.

It is provided as a service to interested stakeholders. The posting of this document does not constitute endorsement by Health Canada, European Commission, Japan Ministry of Health and Welfare or the United States Food and Drug Administration.

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Introduction

The International Cooperation on Cosmetic Regulation (ICCR) initiative is a group of cosmetic regulatory authorities from the United States, Japan, the European Union and Canada. The purpose of the multilateral framework of the ICCR is to maintain the highest level of global consumer protection, while minimizing barriers to international trade.

Nanotechnology has been an ongoing topic of discussion at ICCR since its inaugural annual meeting in 2007. A special "International Workshop on Regulatory Issues Regarding the Use of Nanotechnology in Cosmetics" was convened in Ispra, Italy in July 2009. Hosted by the European Commission's Joint Research Centre, its purpose was to share the current approaches and knowledge on nanomaterials in cosmetics, and to more thoroughly explore the challenges of regulating them. One of the two break-out sessions of this workshop aimed for a nano "Definition—Substance Identification, Detection and Characterization", which concluded[10]:

> *Overall the group agreed that a complete characterization, as would be needed for the scientific characterization of nano-materials within a hazard identification and risk assessment framework, was far more detailed than that needed within a regulatory framework. It was agreed that for regulatory purposes simpler criteria, like those advanced within the ICCR framework would be sufficient. Even so additional work would be needed to fully clarify terminology like stable, insoluble, or size (1 to 100 nanometers?).*

The outcomes of the Ispra workshop were reported and discussed at the 4th annual ICCR meeting (ICCR-4), in September 2009 in Tokyo, Japan[11]. While recognizing that a number of international authorities, including OECD and ISO, are working on definitions of

[10] "Outcome of the International Workshop on Regulatory Issues Regarding the Use of Nanotechnologies in Cosmetics", European Commission, Joint Research Centre, Institute for Health and Consumer Protection, Ispra (Italy), 8–9 July 2009.

[11] A more comprehensive discussion of the outcomes from this and previous meetings may be found at the European Commission's website at: http://ec.europa.eu/enterprise/sectors/cosmetics/cooperation-trade/international-level/; Health Canada's website at: www.hc-sc.gc.ca/cps-spc/person/cosmet/info-ind-prof/iccr-eng.php; Japan's Ministry Health, Labor and Welfare website at: www.mhlw.go.jp/bunya/iyakuhin/keshouhin/iccr03.html; and U.S. FDA's website at: www.fda.gov/Cosmetics/InternationalActivities/ConferencesMeetingsWorkshops/InternationalCooperationonCosmeticsRegulationsICCR/default.htm

nanomaterials[12], none focus on whether a particular material falls within the purview of any particular regulatory definition for nanomaterials. Therefore it was concluded that ICCR, with its narrower focus on cosmetics, is in a strong position to establish a set of criteria that are consistent with international definitions but most relevant to cosmetics and one that can become the basis for criteria within the four regions.

In consideration of all above, ICCR regulators and industry agreed to establish an Ad Hoc Working Group to identify and recommend a set of criteria to help determine if a specific material, used in cosmetics, is to be considered a "nanomaterial" for regulatory purposes and that these criteria, and the results of future ICCR works on nanomaterials, will be taken into account by Regulators when considering future regulations in each region.

It was generally agreed during ICCR-3 that, as a first step in establishing the Ad Hoc Working Group (the Working Group), the critical skills needed to establish criteria needed to be defined.

With that in mind, the Associations Nanotechnology Working Group advanced a critical skills proposal that was endorsed by all ICCR members during the quarterly conference call of November 17, 2009. This became the foundation for selection of individual experts. Experts were nominated and a Working Group established.

During the first meeting of the Working Group, it was agreed to begin by undertaking a comprehensive review of existing definition for nanomaterials. Twenty four relevant definitions were identified and summarized. (Table 2) After careful deliberations by the Working Group members and using the summary table as the primary basis for discussion, the Working Group agreed to criteria for determining whether a material being used in a cosmetic is considered a "nanomaterial" for regulatory purposes.

[12] As examples: ANSI-NSP (American National Standards Institute); www.ansi.org; ASTM (American Society for Testing and Materials): Committee E56; www.astm.org; ISO (International Standards Organization): Technical Committee 229, at www.iso.org/iso/iso_technical_committee.html?commid=381983; and OECD (Organisation for Economic Cooperation and Development) Working Party on Manufactured Nanomaterials; www.oecd.org/department/0,3355,en_2649_37015404_1_1_1_1_1,00.html

Criteria[13]

For purposes of the International Cooperation on Cosmetic Regulation, a substance used in a cosmetic is considered a nanomaterial if it is an insoluble ingredient, intentionally manufactured, with one or more dimensions in the realm of 1 to 100 nanometers in the final formulation and is sufficiently stable and persistent in biological media to allow for the potential of interaction with biological systems.

Discussion

Insoluble and Stable:

The Working Group believes that nanomaterials should be sufficiently stable and persistent in biological media to allow for the potential of interaction with biological systems. This would include nano-carriers intended to enhance dermal penetration if they remain sufficiently stable upon application. Labile nanomaterials, which disintegrate completely upon application to skin into their molecular components (e.g. microemulsions, nanoemulsions, or labile liposomes), should be excluded. This is consistent with several international bodies including the EU[14] , VCI[15], SCCP[16] and SCENIHR[17].

[13] The Working Group felt it important to note that definitions should not be applied overly broadly and in particular should not be used to implicitly, or explicitly, suggest any conclusion as to the safety of the materials covered. Further, the criteria must be interpreted within the context of the discussion provided within the document.
[14] Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products, OJ L 342, of 22.12.2009, p. 59, http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:342:0059:0209:EN:PDF
[15] Verband der Chemischen Industrie e.V. (VCI) www.vci.de/
[16] Scientific Committee on Consumer Products; "SCCP Opinion on Safety of Nanomaterials in Cosmetic Products", Adopted by the SCCP after the public consultation on the 14th plenary of 18 December 2007.
[17] Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), "The appropriateness of existing methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnologies." March 2006.

Additionally, nanomaterials should be insoluble in water and biological media. For example, the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) in its March 2006 report, states that many nanomaterials will have considerable solubility and for "these materials the interaction with living systems remains close enough to the bulk chemical agent to justify the use of well established toxicological testing procedures and approaches." In this context, "insoluble" refers to a material that retains a non-deformable size and shape, when not confined, and does not disintegrate in aqueous solution to ionic or molecular forms.

Manufactured Intentionally:

The Working Group felt it is important that nanomaterials should be the product of nanotechnology. Namely, a nanomaterial should be one where deliberate and knowledgeable processing, at the nanoscale, provides desired finished product functionality with batch to batch uniformity. This would exclude unintentional by-products of reactions that may contain nanoscale materials. Materials with broad distributions of molecule size that may extend into the nanoscale would also be excluded unless the conditions are intentionally manipulated to enhance the proportion in the nanoscale range. By way of example, the UK Department for Environment, Food and Rural Affairs, in its Voluntary Reporting Scheme for engineered nanoscale materials indicated interest is in materials that "are deliberately engineered (i.e. not natural or unintentional by-products of other processes).[18]" It should be noted that the Working Group is aware some authors have included "properties unique to materials in the nano-range" as a criteria[19]. However in the Working Group's considerations it was concluded that inclusion of "uniqueness" as a criterion was problematic. For example, in many cases, scalable, size dependent behavior is well known and wholly predictable. Increasing surface area and solubility rates with decreasing particle size are only two examples where properties would differ from larger or small particles. As such, one could be led to the completely unsatisfactory answer that everything is "nano", as some parameter is size dependent and thus a unique phenomenon. However the Working Group agrees that size alone is insufficient and some distinguishing property of the material should be included. The Working Group

[18] United Kingdom, Department for Environment, Food and Rural Affairs; "UK Voluntary Reporting Scheme for Engineered Nanoscale Materials", found at www.defra.gov.uk

[19] For example Health Canada's working definition includes "exhibits one or more nanoscale phenomena."

believes this can best be captured not by a simple change in property but by explicit consideration of intent—namely deliberate and knowledgeable processing, at the nanoscale, providing desired finished product functionality (i.e. intentionally manufactured).

Size:

The Working Group also questioned the inclusion of precise size limitations. While the scientific unit "nano" is quite precisely defined as a unit measure[20], its physiological significance is far from clear. Indeed, it should be emphasized that there is no established specific risk attributed to nanotechnology and size alone is not in itself an indicator of toxicity.[21] There is no supporting evidence which provides for a bright line size limitation with respect to biological activity. Indeed, for mechanical systems, scaling laws are quite accurate on the nanoscale. This is not the case for electromagnetic properties where many scaling laws fail dramatically and predictions have shown variable accuracy in thermal systems.[22] By example the National Nanotechnology Initiative (NNI), in its definition, uses the modifier "understanding and control of matter at dimensions of *roughly* 1 to 100 nanometers, where unique phenomena enable novel applications[23]". As another example, David Rejeski, Director, Project on Emerging Nanotechnologies has used "*in the realm of* 1-100 nanometers[24]". Therefore the Working Group agrees with these examples and concluded the size should be made an approximation.

The Working Group could find no particular justification for the 100 nm maximum suggested in numerous other definitions. Many of the properties cited as most significant, like surface area or number of particles per unit of mass, follow scaling relationships based on classical continuum models throughout the range of interest, while biological activity is not as straight forward or may even be reversed[25]. In some cases, the critical length scale for

[20] 10^{-9} meter. Introduced in 1951, the nanometer replaced the millimicron. One nanometer equals 0.001 micrometer or 10 angstroms. The prefix comes from the Greek word nanos, dwarf.
[21] Stern S, et al., "Nanotechnology Safety Concerns Revisited." Tox. Sci. 2008, 101:4-21.
[22] K. Eric Drexler "Nanosystems: Molecular Machinery, Manufacturing, and Computation", Wiley and Sons, 1992. Found at www.e-drexler.com/d/06/00/Nanosystems/toc.html#c2
[23] NNI definition found at: http://www.nano.gov/html/facts/whatIsNano.html
[24] Michael Taylor, "Does FDA Have the Tools It Needs? Regulating The Products of Nanotechnology", Woodrow Wilson Center Project on Emerging Nanotechnologies, PEN #5, Oct. 2006.
[25] See Reference 16 and David B. Warheit, et.al, "Pulmonary toxicity study in rats with three forms of ultrafine-TiO2 particles: Differential responses related to surface properties", Toxicology 230 (2007) 90–104.

novel properties and phenomena may be under 1 nm (e.g., manipulation of atoms at ~ 0.1 nm) or be larger than 100 nm (e.g., nanoparticle reinforced polymers have the unique feature at ~ 200-300 nm as a function of the local bridges or bonds between the nanomaterials and the polymer)[26]. As the size range is not grounded by a chemical or biological underpinning, it's not surprising that other groups have adopted differing ranges. For example, the UK Department for Environment, Food and Rural Affairs, in its Voluntary Reporting Scheme for engineered nanoscale materials has defined nanoscale materials as having two or more dimensions up to 200 nm[27], and the Royal Society selected a size range typically from 100 nm down to the atomic level (approximately 0.2 nm)[28].

However, in recognition of the value of a uniform, if arbitrary, limit the Working Group accept the more commonly referenced range for nanomaterials[29] [30] [31]; ***in the realm of 1 to 100 nm, in the final formulation.***

While it is recognized that available methodologies will in many cases not allow direct measurements of the particle size in formulated products, the methodology selected for characterization should reflect the size as used, rather than at other life stages. (i.e., point of manufacture.).

Selection of a measurement technique to characterize nanomaterials is dependant on the nature of the particles. Pre-dispersed, low concentration, mono-dispersed particles require a different treatment than the characterization of powder or highly aggregated and agglomerated systems. In addition to the selection of a technique, sample preparation is a key

[26] Nanotechnology definition (NSET, February 2000) found at: www.nsf.gov/crssprgm/nano/reports/omb_nifty50.jsp
[27] United Kingdom, Department for Environment, Food and Rural Affairs; "UK Voluntary Reporting Scheme for engineered nanoscale materials", found at www.defra.gov.uk
[28] The Royal Society & the Royal Academy of Engineering,"Nanoscience and nanotechnologies: opportunities and uncertainties", July 2004.
[29] NIOSH; Nanoparticles are particles having a diameter between 1 and 100 nm. www.cdc.gov/niosh/nas/RDRP/appendices/chapter7/a7-2.pdf
[30] EPA; nanoparticle (a collection of tens to thousands of atoms measuring about 1-100 nanometers in diameter) is created atom by atom, and the size (and sometimes shape) of the particle is a controlled by experimental conditions. http://epa.gov/ncer/nano/questions/index.html
[31] ASTM; nanoparticle, n—in nanotechnology, a sub-classification of ultrafine particle with lengths in two or three dimensions greater than 0.001 micrometer (1 nanometer) and smaller than about 0.1 micrometer (100 nanometers) and which may or may not exhibit a size-related intensive property. Found at: www.astm.org/Standards/E2456.htm

parameter to consider in the development of a standard operating procedure. The standard operating procedure must provide details of sample preparation and operating conditions of the equipment. The characterization of nano particulate systems can be further improved by comparing particle size results from a number of techniques. For example, particle size results obtained by light scattering can be compared with size results obtained by microscopy. Only then, when consistency is achieved between techniques, or a discrepancy can be explained, can confidence be gained that a system has been correctly characterized[32]. Table 1 provides a summary of the most commonly used techniques to characterize nanomaterials.

Agglomerates and Aggregates:

Any discussion of criteria would not be complete without addressing the issue of agglomeration and aggregation. Due to large unbalanced surface forces, primary nanomaterials tend to aggregate or agglomerate to form larger structures. In aggregates the primary particles are bound strongly by covalent or metallic bonds. The aggregates may also form larger agglomerates, held together by weak forces, such as Van der Waals forces. The formation of agglomerates may be reversible under certain chemical/ biological conditions but an aggregate will not give off primary particles under normal circumstances of use or handling.

Other properties may be affected by these phenomena. For example, the surface area of agglomerates is similar to the sum of its individual components, whereas the external surface area of aggregates may be significantly smaller than the sum of surface areas of the individual components, although still larger than bulk equivalents.

Understanding the behavior of nanomaterials, as sold and used, is critical in characterizing a material for purposes of safety assessment. As an example, stable aggregates, of primary particles in the < 100 nm range may be larger than 100 nm, directly affecting the ability to penetrate biological barriers due to larger size. As such they are likely to behave more like a

[32] K. Schilling et al., "Human safety review of 'nano' titanium dioxide and zinc oxide." Photochem. Photobiol. Sci., 2010, 9, 495.

bulk material with a larger surface area. Additionally the formation of unstable agglomerates may erroneously exclude nanomaterials that have measured sizes > 100 nm in the powder, as sold, but would be smaller in finished formulations.

To address this concern, a volume specific surface area (VSSA) based criterion has been proposed by Kreyling et al.,[33] which regards any particulate material with a specific surface area of ≥ 60 m^2/cm^3, a nanomaterial. This will include materials composed of primary nanomaterials as well as agglomerates or aggregates.

It should also be noted that the degree to which the nanomaterial has formed agglomerates or aggregates is intended to reflect the material behavior in final formulations. Additionally, the volume specific surface area approach, while helpful in characterizing nanomaterials, has the potential to include materials not widely regarded as "nano"; for example, many coated titanium dioxide pigments, even though they are over 200 nm in diameter. (See note in Table 1 -- Agglomerates/Aggregates.)

As such, measurement of size should account for the possibility of stable agglomerates in the solid state fracturing under the shear forces of formulation. (See note in Table 1 -- Agglomerates/Aggregates.)

While the Working Group agrees that that the issues around differences between primary particles, agglomerates and aggregates are most appropriately addressed within a risk assessment framework, it is also important that the criteria try not to identify irrelevant materials.

[33] Kreyling, W.G., Behnke, M., and Chaudhry, Q. (2010, in Press) "A Complementary Definition of Nanomaterial," Nano Today.

Conclusion

The Ad Hoc Working Group on Nanotechnology is pleased to provide the ICCR members with this guidance document intended to help the regulated community determine if a specific material, used in cosmetics, is to be considered a "nanomaterial" for regulatory purposes.

The Working Group wishes to emphasis that the criteria were developed specifically for this purpose and should not be applied overly broadly. In particular these criteria can not be used to implicitly, or explicitly, suggest any conclusion as to the safety of these materials. Furthermore, these criteria can neither be used as a surrogate for hazard identification nor, without consideration of exposure, can they replace a thoughtful risk assessment in determinations of a materials safety.

While the Working Group believes this guidance will be helpful it should also be noted that a number of expert bodies, including ISO and OECD, are working on establishing criteria and definitions of nanomaterials for a variety of purposes and the state of science is also advancing rapidly. As such, this guidance should be applied with flexibility, allowing the criteria to be modified in the future to reflect the best science available.

APPENDIX 1

Methods for Detection and Characterization of Nanomaterials

When carrying out basic characterization of nanomaterials, it is crucial to determine the main properties that can be important in determining their behavior and interactions with biological systems. A list of key properties has recently been published by both the OECD's Working Party on Manufactured Nanomaterials[34] and the FDA's Center for Drug Evaluation and Research (CDER), Office of Pharmaceutical Science[35], which provide a useful guide to the properties for characterization of nanomaterials. A number of methods are also currently available that can be employed to determine these parameters. While other important properties may be identified and the other common techniques may be valid, a brief summary is provided in Table 1.

It is important to note at the outset that:

- There is currently no "gold standard" technique for nanomaterial characterization. While validated methods and instruments are under development, and can be expected to be available in the future, a careful choice and use of an existing method should provide sufficient data for characterization of nanomaterials in the meantime.
- The reproducibility and accuracy of any of the methods used for nanomaterial characterization are largely dependent on sample preparation and calibration of the analytical tools against appropriate standards.
- Results of different measurement techniques may not be directly comparable. This is because some techniques measure individual nanomaterials, often referred to as crystals or primary particles, while others measure aggregates and/or agglomerates. Some techniques further require samples to be dispersed, and/or diluted. It is, therefore, important to ensure consistency in sample preparation to allow direct comparison of results.

[34] OECD, "Guidance Manual For The Testing Of Manufactured Nanomaterials: OECD's Sponsorship Programme; First Revision" ENV/JM/MONO(2009)20/REV, June 2, 2010.
www.olis.oecd.org/olis/2009doc.nsf/LinkTo/NT00009C1A/$FILE/JT03284642.PDF

[35] FDA Center for Drug Evaluation and Research, Office of Pharmaceutical Science (OPS); "Manual of Policies and Procedures (MAPP) entitled Reporting Format for Nanotechnology-Related Information in CMC Review", MAPP 5015.9; June 3, 2010.
www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM214304.pdf

- Compared with characterization of raw materials, methods for characterization of nanomaterials in final formulations may not be straightforward or even available at present. Achieving a reliable, meaningful measurement of size in a finished formulation is often very difficult. For example, in finished formulations a distribution of aggregates and agglomerates, larger than the nano range, may exist and the method of analysis requiring a dry sample, or alternatively a heavily diluted sample, will affect this distribution. Thus, what is measured may therefore not necessarily be a representative of the nanomaterial form in the formulation. In emulsion systems, the results may further be confounded by the size of the emulsion droplets. Depending on the nature of a formulation, it may be feasible to extract/ purify the nano-fraction which can then be characterized. Where measurements in the final formulation are not possible, a fallback position may be to carry out measurements in dispersions/ pre-dispersions.
- It is currently difficult to distinguish very low levels of materials that exist naturally, or as a contaminant in the environment, from purposely-introduced nanomaterials. Some methods (e.g. stable isotope analysis) can be employed to establish background level of a material to distinguish from the purposely-introduced nanomaterials.

  Currently available methods for detection and characterization of nanomaterials are mainly based on light scattering, microscopy, spectrometry, chromatography and other size separation methods, surface characterization methods, and their different variants and combinations. The usefulness and limitations of each method, however, needs to be considered, for example:
  - Light scattering methods are commonly used to measure particle size and provide a distribution of nano particles, agglomerates and aggregates. However analysis by light scattering methods requires a case-by-case approach. For example, Dynamic Light Scattering (DLS) is not appropriate for measuring the size of highly aggregated, broad distribution TiO2 particles, but is very well suited to characterize low concentration monodispersed systems. Also, like other methods, measurement of particle size by light scattering is highly dependent on sample preparation and in most cases is limited to raw ingredients as opposed to final formulation for the reasons outlined above.

- Microscopic methods (AFM, SEM, and TEM) are useful in visualizing nanomaterials as well as determining their structural features—such as size, aggregation state, structure, shape etc. TEM requires very thin specimens for the electrons to pass through. TEM also requires vacuum conditions, and therefore can not handle liquid samples. To overcome this, cryogenic-TEM has been used that can handle frozen samples. The use of Wet-SEM has also been reported[36] (Tiede et al., 2008), which can handle liquid samples in a specially designed capsule and can thus allow characterization of formulated nanomaterials. Scanning probe microscopy tools, such as AFM, can be used to examine liquid samples. The microscopy methods have a current limitation in terms of image analysis—which may pose a bottleneck if analysis of a large number of samples is required.
- HDC (connected to UV/visible spectroscopy, or dynamic light scattering) is a useful method for sizing nanomaterials. Particle separation in HDC takes place in an open channel without a stationary phase through application of a field which controls particle velocity in a narrow channel (such as centrifugal force in the case of sedimentation FFF, or a hydrodynamic flow perpendicular to the separation flow in the case of flow FFF).

[36] Tiede, K., Boxall, A.B.A., Tear, S.P., Lewis, J., David, H. and Hassellov, M. (2008) Detection and characterization of engineered nanomaterials in food and the environment, Food Additives and Contaminants 25(7):795-821.

Table 1

Currently available methods for characterization of nanomaterials

Parameter	Method
Chemical composition	Mass spectrometry, EDX, NMR, and other analytical methods
Size and size distribution	Electron microscopy (AFM, TEM, SEM) Chromatography (FFF, hydrodynamic chromatography, size exclusion), Centrifugation (ultracentrifugation), Mass Spectrometry (SPMS, ICP-MS for metals), XRD (crystal size), SMPS, STXM, CPS, Brookhaven X-Ray Disc centrifuge, Light Scattering, PCCS
Agglomeration/ aggregation	Electron microscopy (AFM, TEM, SEM, STEM) Spectroscopy (XRD), BET Light Scattering (Brookhaven X-Ray Disc Centrifuge, PCCS, Laser Diffraction) It should be noted that techniques such as DLS and CPS may conclude that materials are > 100 nm but TEM would show this is the result of agglomerates of the aggregates. The measurement of particle size may be done conducted by CPS, but it is important to assure that pre-dispersed powders are subjected to shear forces similar to those that will be encountered during the final application of the material.
Mass concentration	AEM, CFM Gravimetric methods, Centrifugal Sedimentation
Particle number	Particle counters
Shape	Electron Microscopy (AFM, TEM, SEM) Chromatographic (SedFFF-DLS), XRD, STXM
Surface chemistry	AEM, CFM UV/Visible spectrometry, XPS, IR, Raman
Surface charge	Chromatography (e.g. capillary electrophoresis), Zeta potential
Surface area	BET

Parameter	Method
Solubility/ dispersibility	Water solubility, log K_{ow}
Stability	The system should be monitored over a period of time to ensure the particles have not changed their state of aggregation/ agglomeration. For example, the stability of particles in dispersion could be assessed over a period of 2-3 years by UV-Vis spectroscopy to ensure dispersion stability.

AEM – Analytical Electron Microscopy (a combination of analytical tools, such as spectroscopy, and electron microscopy for composition analysis).

AFM – Atomic Force Microscopy

BET – Brunauer Emmett Teller method based on nitrogen absorption

CFM – Chemical force microscopy (a recent development in scanning probe microscopy that can enable identification of chemical nature of materials, Tiede et al., 2008)

CPS – Centrifugal Particle Sedimentation

DLS – Dynamic light scattering

EDX – Energy Dispersive X-ray spectroscopy

FFF – Field Flow Fractionation

ICP-MS – Inductively coupled plasma mass spectrometry

NMR – Nuclear Magnetic Resonance

PCCS – Photo Cross Correlation Spectroscopy

SEM – Scanning Electron Microscopy

SMPS – Scanning Mobility Particle Sizing

SPMS – Single Particle Mass Spectrometry

STEM – Scanning Transmission Electron Microscopy

STXM – Scanning Transmission X-ray Microscopy

TEM – Transmission Electron Microscopy

XPS – X-ray Photoelectron Spectroscopy

XRD – X-ray diffraction

Table 2

Summary of current definitions for Nanotechnology, Nanoscale, and Nanoparticles

Organization	Size (nm)	Dimensions	Manufactured	Insoluble	Unique Property	Surface Area	Other
ASTM[i]	> 1– < ~ 100	2 or 3	Not Included	Not Included	May or may not	Not Included	
British Institute of Standards (BSI)[ii]	1–100	1 or more	Not Included	Not Included	Not Included	Not Included	
CEPA[iii]	1–100	1 or more	Yes	Not Included	Yes	Not Included	
Health Canada[iv] (Working Definition)	1–100	1 or more	Yes	Not Included	Yes*	Not Included	*Unique properties even if < or > than 1–100 nm
DEFRA[v]	< 200	2 or 3	Not Included	Not Included	Not Included	Not Included	
EPA (PPDC)[vi]	1–100	Not Included	Yes	Not Included	Not Included	Not Included	
EU Cosmetics Regulation (Article 2 Definitions (k))[vii] Also see the provision[viii]	1–100	1 or more	Yes	Yes	Not Included	Not Included	Also biopersistant

Organization	Size (nm)	Dimensions	Manufactured	Insoluble	Unique Property	Surface Area	Other
EU Novel food Regulation (Article 3 Definitions (c))[ix] (legal definition —not finally adopted yet)	< 100*	1 or more	Yes	Not Included	Yes	Not Included	*Includes aggregates and agglomerates if unique properties
European Medicines Agency (EMEA)[x]	0.2–100	Not Included	Not Included	Not Included	Not Included	Not Included	
European Food Safety Authority (EFSA)[xi]	< 100	Not Included	Not Included	Not Included	Not Included	Not Included	
FDA[xii]	Not Included	Not Included	Not Included	Not Included	Not Included	Not Included	
Friends of the Earth[xiii]	< 100	1 or more	Not Included	Not Included	Yes	Not Included	
ISO WG 229[xiv] (Working Draft)	< 100	Not Included	Not Included	Not Included	Not Included	Yes	Crystal, mass fraction
ISO TS 27687[xv]	1–100	Not Included	Not Included	Not Included	Yes	Not Included	
NIOSH[xvi]	1–100	3*	Not Included	Not Included	Not Included	Not Included	*Particle diameter
NNI[xvii]	1–100	Not Included	Not Included	Not Included	Yes	Not Included	

Organization	Size (nm)	Dimensions	Manufactured	Insoluble	Unique Property	Surface Area	Other
OECD[xviii]	< 100	Not Included	Yes*	Not Included	Yes	Not Included	*Implied
Royal Society[xix]	Not Included	Not Included	Yes	Not Included	Not Included	Not Included	
SCCP[xx]	< 100	1 or more	Not Included	Yes	Yes	Not Included	
SCENIHR[xxi]	< 100	1 or more	Yes	Not Included	Not Included	Yes*	*60 m^2/g
US Nanoscale Science, Engineering and Technology (NSET) Subcommittee of the National Science and Technology Council's Committee on Technology (February 2000)[xxii]	Not Included*	Not Included	Not Included	Not Included	Yes	Not Included	*May be < 1 or > 100
UK Royal Society & Royal Academy of Engineering[xxiii]	0.2–100	Not Included	Not Included	Not Included	Not Included	Not Included	
VCI[xxiv]	1–100	2 or 3	Yes	Yes	Not Included	Yes	

[i] ASTM International (ASTM). ASTM E2456 - 06 Standard Terminology Relating to Nanotechnology.
[ii] British Institute of Standards (BIS). Vocabulary—Nanoparticles. Publicly Available Specification (PAS) 71, pp. 1-2 (2005).
[iii] Environment Canada. Proposed Regulatory Framework For Nanomaterials Under The Canadian Environmental Protection Act, (CEPA)1999.

[iv] Personal Communication from Ms. Carter-Phillips.

[v] United Kingdom Department for Environment Food and Rural Affairs (DEFRA). UK Voluntary Reporting Scheme for engineered nanoscale materials.

[vi] United States Environmental Protection Agency (EPA). Nanotechnology and Pesticides.

[vii] European Commission. Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products, OJ L 342, of 22.12.2009, p. 59.

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